

REMARKS

Claims 60-141 were pending, and claims 1-59 were canceled without prejudice or disclaimer. Claims 67-141 were withdrawn. Claims 60-66 were rejected. After entry of the amendments and remarks herein, claims 60-66 are pending. Claim 60 is herein amended.

Amendments to the claims are made to point out more specifically and claim distinctly the subject matter regarded as invention. Such amendments should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

No new matter has been added by virtue of the amendments, support being found throughout the specification and claims as originally filed. Specifically, support for the amendments to claim 60 may at least be found in the filed specification at page 6, lines 8-9. Reconsideration is requested, at least for the reasons discussed herein.

Rejection of the claims under 35 U.S.C. §112, first paragraph, written description

Claims 60-66 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully disagree and traverse the rejection.

MPEP §2163, citing *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976), indicates that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed and that the Office has the initial burden of ***presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims***. [Emphasis added] Applicants submit that the Office has not presented any evidence or reasoning why persons skilled in the art would not recognize in Applicants' disclosure a description of the claimed invention.

Nevertheless, without acquiescing to the rejection and to expedite prosecution, claim 60 has been amended to recite that "the sample of semen is collected as an ejaculate" and that "the window of time after ejaculation ... is determined." Thus,

amended claim 60 is directed to a method for treating a specimen of semen containing sperm cells to increase the relative number of sperm cells of a preferred sex type. The method entails collecting a sample of semen as an ejaculate, holding the semen after collection for a predetermined period of time, and after the predetermined period of time, separating the semen into two components; a first component having a higher number of sperm of the preferred sex type and a second component having a higher number of sperm of the non preferred sex type relative to sperm of the preferred sex type. The separation step is performed in a window of time after ejaculation that is determined by locating a maximum (e.g., maximum percent of female cells) in a curve obtained by plotting the percent of female cells determined by FISH against the percent cells that are Koo positive for aliquots of a sample wherein separation is performed at varying times of incubation after collection, thereby determining the time at which the maximum percent female cells occurs. Furthermore, the claimed separation step begins no earlier than about one hour before the time of the maximum percent of female cells.

Specifically, the Office Action at page 4 states that “the claims encompass separating a sample in a desired window of time to achieve a maximum of female cells, which has been determined by FISH, for which no written description has been provided.” Applicants respectfully invite the Examiner’s attention to the filed specification at page 5, lines 5-10, which states:

In other embodiments of the invention, the window of time for separation or sexing is determined by locating a maximum in the curve obtained by plotting percent female cells determined by fluorescent in situ hybridization (FISH) against percent Koo positive cells, determining the time at which the maximum percent female cells occurs, and beginning the separation step no earlier than about one hour before the time of the maximum percent female cells.

Thus, the specification clearly and plainly shows that Applicants were in possession of this particular embodiment of the invention.

The Office Action asserts that: “It is not described in the specification how one sample to be separated into two components can differ in the amount of female vs. male cells over time and how that maximum time is particularly determined...” and that

“Applicant appears to be claiming using the FISH analysis to track when more female sperm cells are present in a single sample, for which there is no scientific support . . .”

Applicants are not asserting that an **unseparated** sample differs in the amount of female vs. male cells over time, although this may be possible (e.g., preferential cell death of female or male cells). Rather, the amounts (percentages) of female vs. male cells differs over time when a **sample has been separated into a female cell component and a male cell component**; e.g., **a result of Y-bearing sperm's (male sperm's) ability to adhere to cell binding agents (e.g., H-Y binding agents, e.g., Koo antibody) in greater proportion than X-bearing sperm (female sperm) and the discovery that this difference is most pronounced at a particular time after collection.**

Thus, this discovery allows for the **greater separation** of Y and X-bearing sperm when the separation procedure is performed at a time when the binding agent binds Y-bearing sperm in greater proportion than X-bearing sperm. This differential binding ability of Y- vs. X- sperm is evident throughout the application as filed, and is specifically illustrated in Example 1 and the related data of Tables 1 & 2. The paragraph at page 4, lines 5-10 of the filed specification explains this discovery:

We have discovered that there is a period of time, i.e., a sexing window, during **which Y-chromosome bearing sperm develop an ability to adhere or bind to cell binding agents in greater proportion than X-chromosome bearing sperm**. If the spermatozoa are treated with a cell binding agent in this window, Y-chromosome bearing sperm will adhere or bind preferentially to a cell binding agent whereas X-chromosome bearing sperm will remain preferentially in the fluid. Thus, **separating the cell binding agent with preferentially bound Y-chromosome bearing sperm will remove Y-chromosome bearing sperm preferentially leaving a higher percentage of X-chromosome bearing sperm, thereby biasing the remaining non bound sperm for producing female offspring when introduced into a suitable fertile mammal.** [Emphasis added]

The reason for Y-sperm's preferential binding to binding agents and, in particular, the change in this binding over time is not fully understood, but understanding how this change occurs is not necessary for patentability.

The Federal Circuit has held that an inventor need not understand how his invention works (*Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), "... it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. § 112." (at 741, footnote 3), citing *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983)).

Nonetheless, while not being bound by theory, it is hypothesized that this change in binding (e.g., Koo antibody binding) over time may be the result of one or more of the following; increased expression of the Koo antibody's antigen post collection, continued development of the "sticky patch" (See paragraph 28 of the publication), unmasking of a binding antigen on the cell (e.g., through the loss of another molecule which masks the binding antigen). Thus, the application clearly teaches how the ratio of male to female sperm cells can change in sperm samples that have been fractionated by binding agents at various times after a post collection incubation step.

The Examiner stated that the specification does not describe how a maximum time is determined. Applicants respectfully disagree. The application fully describes how a maximum of time is determined. In particular this is evident in Examples 1 and 3 and the detailed protocols starting at page 25 of the filed specification and continuing to page 39.

The paragraphs at page 4, lines 19-31, of the filed specification teaches how to identify when the maximum in time occurs and how the maximum in time can be determined by Koo staining::

The window opens when a sufficient number of sperm cells exhibit the sticky patches so that separation preferentially removes sufficient Y-chromosome bearing sperm so that the remaining non bound sperm is biased to a desired level with X-chromosome bearing sperm. **The window closes when a sufficient number of sperm cells exhibit the sticky patches so that separation can no longer provide the desired biased level.** [Emphasis added]

In certain preferred embodiments of the invention, the window opens with the appearance of the sticky patches on at least about 20% of the sperm cells in the semen, preferably at least about 25%, and more preferably at least about 30%, **as determined by labeling the sperm with Koo antibody**. The window closes when more than more than 40% of the sperm cells have sticky patches, preferably more than 35%, **as determined by labeling the sperm with Koo antibody**.

The Examiner also asserts that, "it appears as if the FISH analysis is merely a measure of time and temperature compared to the staining process, i.e., the optimum time and temperature at which the ICC positive cells are stained" That the time and temperature are variables of FISH staining is incorrect. In contrast, the variables of time and temperature correspond to the incubation of the semen specimen.

All Koo and FISH staining were performed under **consistent time and temperature conditions** (See Example 1). For example, **there is no difference in the conditions (temperature or time) in which the Koo staining protocol was performed on the sample taken at either the two hours post collection or 12 hours post collection times (See Tables 1 and 2)**. The only variable is the time at which the semen specimen is incubated (prior to contacting with the binding agent or staining agent) at a constant temperature post collection **but before staining**.

The Examiner also takes issue that the "applicant merely analyzes the **already** separated samples at different temperatures and time in examples 1 and 2 by FISH" [Examiner's emphasis] and "... the examples provided do not support [sic] such as determination nor a method of analyzing the percent female cells before the separation step." Another means by which to determine a maximum is by determining the time point when the maximum percent of female cells is obtained in a test sample (e.g., by FISH) that **has been separated into unbound and bound fractions**. This identified maximum for female sperm cell enrichment is then later used for the actual enrichment of female sperm cells. Nevertheless, although Examples 1 and 2 show the analysis of separated samples, it would be apparent to one of ordinary skill in the art that the experiments demonstrate and establish a correlation between the percent of Koo positive cells and the percent female cells. Based on this evidence, one of ordinary skill in the art would recognize this observation could be used to identify a window and/or

maximum in time that allows for the **greater separation** of Y and X-bearing sperm, as Applicants have (e.g., at page 41, lines 9-11).

In a preferred embodiment, the maximum is identified by contacting the semen specimens that have been incubated at various times post collection at a constant temperature with a Koo antibody, which preferentially binds the Y-sperm, allowing the separation of the bound sperm from the non-bound sperm which remains in the fluid. FISH may then be performed on the unbound sperm in the fluid (e.g., Table 2) to determine the percent of female sperm cells. When these results are plotted, it is readily apparent that, during a specific window/period of time, the **separated unbound sample** will exhibit a significantly higher percent of X-sperm (female sperm) than Y-sperm (male sperm). This maximum percent of X-sperm is readily apparent on the Koo vs. FISH graphs of Figs. 2-4 which illustrate the data in Table 1 (percent of cells ICC positive with Koo) plotted against the data of Table 2 (percent of female cells in the fluid after separation as assayed by FISH). As observable in each graph there is a point at which the maximum number of X-sperm remain in the **separated unbound fraction** as was determined by FISH. **It is the incubation time point which corresponds to the separated unbound fraction containing the maximum number of X-sperm cells at which performing the separation protocol is optimal in order to enrich for X-sperm.**

In view of the above, it is clear the claims are fully supported by the application as filed. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 60-66, under 35 U.S.C. §112, first paragraph for alleged lack of written description.

Rejection of the claims under 35 U.S.C. §112, first paragraph enablement

Claims 60-66 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully disagree and traverse the rejection.

In support of the rejection of the claims for lack of enablement, the Office Action, at pages 5-6 alleges:

Thus, the claims encompass separating a sample in a desired window of time to achieve a maximum of female cells, which has been determined by FISH, and a method of obtaining either a preferred sample of male or female sperm, for which no scientific support has been provided. It is not described in the specification how one sample to be separated into two components can differ in the amount of female vs. male cells over time and how that maximum time is particularly determined, further, applicant merely analyzes the **already** separated samples at different temperatures and time in examples 1 and 2 by FISH. Thus, it appears as if the FISH analysis is merely a measure of time and temperature compared to the staining process, i.e., the optimum time and temperature at which the ICC positive cells are stained, not a determination of when more female sperm exist in a sample. Applicant appears to be claiming using the FISH analysis to track when more female sperm cells are present in a single sample, for which there is no scientific support or description is provided. Moreover, the examples provided do not support such as determination nor a method of analyzing the percent female cells before the separation step. Thus, in view of the lack of any specific guidance with respect to how a maximum amount of female sperm occurs at a specific time point in one sample, one skilled in the art would expect a trial and error process to determine how such an occurrence is possible with respect to a sample and how determining such would apply to the as disclosed application, and would further have to determine through undue experimentation, without guidance from the specification, how to obtain a window of time when a maximum amount of female sperm exist in a sample. [Examiner's emphasis]

However, the foregoing statements are nothing more than conclusory statements unsupported by any acceptable evidence or reasoning. Moreover, these statements ignore the clear teachings of the application, as discussed in detail above regarding the response to the written description rejections.

Indeed, MPEP §2164.04, citing the court in *In re Marzocchi* (169 U.S.P.Q. 367, 370 (CCPA 1971)), states:

It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure **and to back up assertions of its**

own with acceptable evidence or reasoning which is inconsistent with the contested statement. [Bolted emphasis added.]

MPEP §2164.04 further provides that in cases where doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts:

the examiner should specifically identify what information is missing and why one skilled in the art could not supply the missing information without undue experimentation. ***References should be supplied if possible to support a prima facie case of lack of enablement*** but are not always required. ***However, specific technical reasons are always required.*** [Citations omitted; Emphasis added]

Here, the Examiner fails to explain why she doubts the truth of Applicants' assertion that a semen sample can be separated into two components enriched for sperm of a sex type using a window of time after ejaculation (e.g., determined by locating a maximum in a curve obtained by plotting percent female cells determined by FISH against percent Koo positive cells), and fails to provide acceptable evidence or reasoning as to why Applicants' assertion is not true. The Examiner has not only failed to supply references but does not even proffer technical reasons, which the MPEP indicates are always required.

The Examiner goes to great lengths to point out information that is allegedly missing from Applicants' disclosure but makes absolutely no showing as to why one skilled in the art could not supply the missing information without undue experimentation. Without more, the Examiner must accept the truth of Applicants' assertions.

In sum, the arguments presented above for the written description rejections address most of the issues the Examiner raised with respect to enablement. Thus, rather than reargue the arguments presented above Applicants direct the Examiner to the above arguments which support both written description and enablement of the claims, only those issues raised in the enablement rejection which are not fully addressed above will be discussed below.

In support of the enablement rejection, the Office Action at pages 6-7 states:

Further, applicants specification, examples, Tables, etc only practice the invention with the female cells being the preferred sex type, not at all enabling one to obtain a preferred **male** sample. Moreover, the examples provided do not support obtaining a preferred male sex type in applicants claimed method. Thus, in view of the lack of any specific guidance with respect to how to obtain a male preferred sex type using applicant method, one skilled in the art would expect a trial and error process to determine how such a preference can be analyzed using such method and how determining such would apply to the as disclosed application, and would further have to determine through undue experimentation, without guidance from the specification, how to obtain a male population using the steps and methods of the invention. [Examiner's emphasis]

Applicants respectfully disagree and travers the rejection.

Based on the teachings in the application and what was known in the art, the application clearly enables one skilled in the art to practice the claimed invention to obtain a preferred male sample. As discussed above, the sperm cell sample can be separated into two fractions (bound and unbound) by utilizing the cell binding agents. In a preferred embodiment, the bound cell fraction preferentially includes Y-sperm and the liquid unbound cell fraction preferentially includes X-sperm. Thus, the application teaches the preferential isolation of both male (Y-sperm) and female cells (X-sperm). In selecting for a preferred male phenotype the binding agent bound sperm is selected for in vitro fertilization rather than the unbound sperm (female). Thus, the techniques for the preferential selection of male vs. female sperm are essentially identical except that the male sperm are obtained from the bound fraction.

The method for obtaining a preferred male sperm fraction is taught thought the application, including, for example, the paragraph at page 6, lines 20-27 of the filed specification: "[t]he desired or preferred sex can vary with application. Also, the selected sperm cells can be either the bound cells or the non bound cells, depending on the application."

Furthermore, the paragraph spanning page 6, line 18 – page 19, line 4 of the filed specification states:

... bound sperm cells also can be recovered, thus, providing separation and isolation of the two populations of spermatozoa (i.e., X-and Y-bearing

sperm). Recovery of the magnetic component is easily performed by removing the separation container from the magnetic separator and then draining the container. **Reversal of the binding is accomplished in the same manner as in certain types of chromatography or antibody-antigen reactions.** [Emphasis added]

Thus, it is clear that, based on the specification and what was known in the art at the time of filing, one of ordinary skill could practice the claimed invention without undue experimentation. In the absence of any showing to the contrary that one skilled in the art could not supply the missing information without undue experimentation, the Examiner must accept the truth of Applicants' assertions.

In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 60-66 under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the enablement requirement.

Rejection of the claims under 35 U.S.C. §102

Claims 60-66 are rejected under 35 U.S.C. 102 over several references cited by the Examiner. Applicants respectfully disagree and traverse the rejections.

In order to anticipate a claim, each and every element of the claim must be found in a single reference (MPEP § 2131). As currently amended, claim 60 recites that "the separating step is performed in a window of time after ejaculation that is determined by locating a maximum in a curve obtained by plotting percent female cells determined by FISH against percent Koo positive cells for aliquots of another semen sample."

Because claims 61-66 depend from claim 60, claims 61-66 also incorporate this feature.

Claims 60, 61, 63 are rejected under 35 U.S.C. 102(b) over Sills et al. (American Journal of Reproductive Immunology, vol. 40, 1998; "Sills"). Sills **fails** to teach or suggest a method

wherein the separating step is performed in a window of time that is determined by locating a maximum in the curve obtained by plotting percent female cells determined by FISH against percent Koo positive cells for aliquots of another semen sample, the aliquots being taken at various times after collection, determining the time at which the maximum percent female cells occurs, and determining the period of time for holding the semen after collection before

and beginning the separation step to provide a time no earlier than about one hour before the time of the maximum percent female cells as determined by FISH.

Because Sills does not teach the feature set forth above, the presently claimed invention is not anticipated by Sills. Further, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art in view of Sills.

Claims 60-62 are rejected under 35 U.S.C. 102(b) over any one of Benjamin (US 6153373), Benjamin (US2003/0068654), or Benjamin (US 6489092). Applicants traverse the rejection. None of the Benjamin references teaches or suggests that a window of time after ejaculation is determined for performing the separation to obtain an increase in the percentage of mammalian offspring of either sex, the increase being compared to separation performed outside the window.

The Benjamin references fail to teach or suggest that such a window can exist. Present Applicants have discovered the existence of a time period for the preferential binding of male sperm to binding agents and how to use it for performing the separation to obtain an increase in the percentage of mammalian offspring of either sex.

Because none of the Benjamin references teach the feature set forth above, the presently claimed invention is not anticipated by any of the Benjamin references. Further, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art in view of any of the Benjamin references.

Claims 60-63 are rejected under 35 U.S.C. 102(b) over Blecher et al (US2001/0041348 A1; "Blecher"). Blecher **fails** to teach or suggest that a window of time after ejaculation is determined for performing the separation to obtain an increase in the percentage of mammalian offspring of either sex. Nowhere does Blecher teach or even suggest that such a window can exist. Present Applicants have discovered the existence of this window and how to use it for performing the separation to obtain the desired increase in the percentage of mammalian offspring of either sex.

Because Blecher does not teach the feature set forth above, the presently claimed invention is not anticipated by Blecher. Further, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art in view of Blecher.

Claims 60-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Zavos et al. (US 4999283). As claims 67-69, 75, and 82 were withdrawn, Applicants only address the rejections against claims 60-62. Zavos et al. **fails** to teach or suggest determining a window of time after ejaculation and using the identified window of time for performing the separation step to obtain an increase in the percentage of mammalian offspring of either sex. Indeed, Zavos et al does not even suggest that such a window can exist. Present Applicants have discovered the existence of this window and how to use it for performing the separation to obtain the desired increase in the percentage of mammalian offspring of either sex.

Because Zavos does not teach this feature, the presently claimed invention is not anticipated by Zavos. Further, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art in view of Zavos et al.

Claims 60-62, 67-69, 73 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Van den Bovenkamp (US 3687806). As claims 67-69, 73, and 74 were withdrawn, Applicants only address the rejections against claims 60-62. Van den Bovenkamp **fails** to teach or suggest determining a window of time after ejaculation and using the identified window of time for performing the separation step to obtain an increase in the percentage of mammalian offspring of either sex. Indeed, Van den Bovenkamp does not even suggest that such a window can exist. Present Applicants have discovered the existence of this window and how to use it for performing the separation to obtain the desired increase in the percentage of mammalian offspring of either sex.

Because Van den Bovenkamp does not teach the feature above, the presently claimed invention is not anticipated by Van den Bovenkamp. Further, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art in view of Van den Bovenkamp.

Rejection of the claims under 35 U.S.C. §103

The Office has also made a number of further rejections under 35 U.S.C. §103, which all rely on the teachings of Sills, Benjamin (US 6153373), Benjamin

(US2003/0068654), Benjamin (US 6489092), Blecher, Zavos, and/or Van den Bovenkamp. However, for at least the reasons above, the combination of the cited references do not render the present claims obvious. None of Sills, Benjamin (US 6153373), Benjamin (US2003/0068654), Benjamin (US 6489092), Blecher, Zavos, and/or Van den Bovenkamp teach or suggest determining a window of time after ejaculation and using the identified window of time for performing the separation step to obtain an increase in the percentage of mammalian offspring of either sex, let alone that the window of time that is determined by locating a maximum in a curve obtained by plotting percent female cells determined by FISH against percent Koo positive cells for aliquots of another semen sample. Nor do the remaining cited references, i.e., Johnson (Reprod. Fertil. 1995) and/or Spaulding (5021244) remedy the deficiencies of Sills, Benjamin (US 6153373), Benjamin (US2003/0068654), Benjamin (US 6489092), Blecher, Zavos, and/or Van den Bovenkamp.

In summary, applicants respectfully argue that the claimed invention of U.S. Patent Application No. 10/723,268 is non-obvious in view of all of the cited references individually or in combination. A combination of the teachings of does not lead to the present invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 60-66 presented herein. If a telephone conference with Applicants' attorney would be useful in expediting prosecution of the application, Applicants invite the Examiner to call the undersigned at the telephone number indicated below. Applicants thank the Examiner in advance for this courtesy.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, the Commissioner is hereby authorized and requested to charge Deposit Account No. **04-1105**, under Order No. 59660 (300541)..

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Respectfully submitted,

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